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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte ROB HOOFT VAN HUIJSDUIJNEN and VINCENT RICHARD

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Appeal 2010-005829
Application 10/590,808
Technology Center 1600

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Before TERESA STANEK REA, Deputy Under Secretary of Commerce for Intellectual Property and Deputy Director of the United States Patent and Trademark Office, LORA M. GREEN, and FRANCISCO C. PRATS, Administrative Patent Judges.

PRATS, Administrative Patent Judge.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to a method of treating coronary obstruction or peripheral vasoconstriction. The Examiner rejected the claims for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

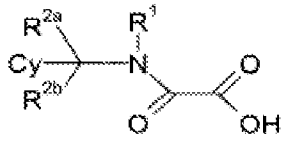
Appellants' invention is directed to using "methylene amide derivatives of Formula (I) for the prevention and/or the treatment of cardiovascular disorders such as coronary obstruction and heart failure, in particular for the prevention and/or treatment of endothelial dysfunction in heart failure" (Spec. 1). The compounds of formula (I) are especially useful "in the treatment of increased peripheral vasoconstriction in chronic heart failure" (id.).

The Specification discloses that, in the prior art, "[s]ubstituted methylene amide derivatives of Formula (I) have been developed as Protein Tyrosine Phosphatase (PTP) inhibitors, particularly Protein Tyrosine Phosphatase 1B (PTP1B) inhibitors for the treatment of metabolic disorders mediated by insulin resistance or hyperglycemia (WO 03/064376)" (id. at 3).

Different from the prior art activities of these compounds, however, the Specification states that examples using mouse models show that "compounds of the invention are able to acutely restore endothelial function in mice with chronic heart failure" (id. at 41).

Claims 1-16, 20, and 21 stand rejected and appealed (App. Br. 2). Claim 1, the only independent claim, is representative and reads as follows:

> Claim 1: A method of treating coronary obstruction or peripheral vasoconstriction in a patient in need thereof, the method comprising administering an



(I)

effective amount of a methylene amide of Formula (I) to treat coronary obstruction or peripheral vasoconstriction in the patient:

as well as its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts and pharmaceutically active derivatives thereof, wherein

R^1 is selected from the group consisting of $(C_1\text{-}C_{15})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, aryl, heteroaryl, (3-8-membered)-cycloalkyl or heterocycloalkyl, $(C_1\text{-}C_{12})$alkyl- aryl or $(C_1\text{-}C_{12})$alkyl-heteroaryl, $(C_2\text{-}C_{12})$alkenyl-aryl or -heteroaryl, $(C_2\text{-}C_{12})$alkynyl-aryl and -heteroaryl;

R^{2a} and R^{2b} are each independently from each other selected from the group consisting of H and $(C_1\text{-}C_{12})$alkyl;

Cy is selected from D and E;

D is selected from the group consisting of thienyl and phenyl, each substituted with a phenyl, oxadiazole; or 1 or 2 moieties selected from the group consisting of -NH-CO-R^3, -SO_2-$NR^3R^{3'}$, and-CO-$NR^3R^{3'}$;

E is selected from the group consisting of aryl, heteroaryl, (3-8-membered)-cycloalkyl and heterocycloalkyl wherein aryl, heteroaryl, (3-8-membered)-cycloalkyl and heterocycloalkyl are substituted by $(C_2\text{-}C_{18})$alkynyl;

R^3, $R^{3'}$ are independently selected from the group consisting of H, $(C_1\text{-}C_{15})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, aryl, heteroaryl, (3-8-membered)cycloalkyl or heterocycloalkyl, $(C_1\text{-}C_{12})$alkyl aryl or heteroaryl, $(C_2\text{-}C_{12})$alkenyl-aryl or - heteroaryl, $(C_2\text{-}C_{12})$alkynyl-aryl or - heteroaryl.

The sole rejection before us for review is the Examiner's rejection of claims 1-16, 20, and 21 under 35 U.S.C. § 103(a) as obvious Liu,[1] Sowers,[2] and Parissis[3] (Ans. 4-6).

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[1] U.S. Patent App. Pub. No. 2002/0035136 A1 (filed August 22, 2001).

OBVIOUSNESS

ISSUE

The Examiner cites Liu as disclosing the claimed compounds and their use in treating a variety of disorders, including "autoimmune diseases, acute and chronic inflammatory diseases, osteoporosis, obesity, cancer, malignant diseases, and type I and type II diabetes" (Ans. 5). The Examiner concedes, however, that Liu "differs from the instant claims insofar as it does not teach treating coronary obstruction or peripheral vasoconst[r]iction" (id.).

To meet that deficiency, the Examiner cites Sowers as teaching that "cardiovascular diseases, including atherosclerosis (coronary obstruction), are a major cause of mortality in persons with diabetes and that hypertension contributes to this high prevalence of cardiovascular disease" and that "hypertension and diabetes serve to exacerbate each other" (id.).

The Examiner cites Parissis for its teaching that "peripheral vasoconstriction is associated with endothelial dysfunction and hypertension, and that patients with hypertension often have a high circulation of endothelin-1, which can result in peripheral vasoconstriction" (id.).

Based on the references' teachings, the Examiner reasons that an ordinary artisan would have considered it obvious to administer Liu's compounds to treat "coronary obstruction and peripheral vasoconstriction,

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[2] James R. Sowers et al., Diabetes, Hypertension, and Cardiovascular Disease: An Update, 37 HYPERTENSION 1053-59 (2001).
[3] John. T. Parissis et al., Plasma profiles of peripheral monocyte-related inflammatory markers in patients with arterial hypertension. Correlations with plasma endothelin-1, 83 INT. J. CARDIOL. 13-21 (2002).

since they are problems associated with diabetes, as taught by Sowers et al. and Parissis" (id. at 6). The Examiner further reasons:

> The artisan would reasonably expect success in treating coronary obstruction or peripheral vasoconstriction in a patient by administering the compounds of Liu to diabetic patients since hypertension and diabetes frequently coexist and each pathophysiological disease entity serves to exacerbate the other, as taught by Sowers et al. Thus, in treating diabetes the artisan would reasonably expect a positive effect on hypertension and cardiovascular disease.

(Id.)

Appellants initially note that their invention is "based on the in vivo data provided on pages 40-41 of the specification, using the coronary artery occlusion model of example 1 wherein mouse [sic, mice] are not required to have diabetes" (App. Br. 5). Appellants contend that the Examiner failed to make a prima facie case of obviousness because the cited references do not "establish that there would have been a reasonable expectation of success without first having had performed the experiments shown in the present specification" (id. at 6).

In particular, Appellants urge, given Sowers' disclosure that treatment of patients with antihypertensive drugs did not reduce progression to diabetes, an ordinary artisan would have understood that "treatment of one disease does not necessarily positively impact[] the other, and can even have a negative outcome on the progression of the other disease" (id. at 7; see also Reply Br. 2-5). Moreover, Appellants argue, in view of Sowers' teaching that cardiovascular disorders may be more difficult to treat in diabetic patients, Sowers "does not provide any indication that using an antidiabetic agent would also treat cardiovascular disease" (App. Br. 7),

particularly given the fact that Liu's compounds act on different biological target molecules than those involved in cardiovascular disorders (see id. at 9).

Thus, Appellants urge, "the only suggestion to do what Appellants have done is Appellants['] own disclosure, i.e. hindsight" (id. at 8). Appellants conclude, therefore, that "the Examiner has not satisfied the Office's initial burden to establish that the claims of this application are unpatentable under 35 U.S.C. § 103(a)" (id. at 10).

The Examiner responds that the "claims as written are not necessarily distinguished from Liu since the claims read on treatment of diabetic patients with hypertension, and/or atherosclerosis. The Sowers reference[] strongly suggests a biological link between diabetes, hypertension and cardiovascular disease" (Ans. 7). Further, the Examiner urges, "[i]t should also be pointed out that the compounds of Liu are useful for treating obesity, also associated with diabetes, hypertension, and cardiovascular disease" (id.).

In view of the positions advanced by Appellants and the Examiner, the issue here is whether the Examiner has made a prima facie case that an ordinary artisan, viewing the teachings of the cited references, would have been prompted to administer the claimed compounds to an individual within the claimed patient set.

FINDINGS OF FACT *("FF")*

1. It is undisputed that Liu discloses compounds encompassed by claim 1.
2. Liu discloses that its compounds are protein tyrosine kinase PTP1B inhibitors (Liu, abstract), and are therefore "therapeutically beneficial

for the treatment of diseases such as type I and II diabetes, obesity, autoimmune disease, acute and chronic inflammation, osteoporosis and various forms of cancer" (id. at [0003]).

3. Sowers discloses:

> Cardiovascular diseases (CVDs) are the major causes of mortality in persons with diabetes, and many factors, including hypertension, contribute to this high prevalence of CVD. Hypertension is approximately twice as frequent in patients with diabetes compared with patients without the disease. Conversely, recent data suggest that hypertensive persons are more predisposed to the development of diabetes than are normotensive persons.

(Sowers 1053 (abstract).)

4. Sowers discloses that, in addition to the common coexistence of both diabetes and hypertension in patients, evidence from clinical studies suggests that "each pathophysiological disease entity, although independent in its own natural history, serves to exacerbate the other" (id. at 1053).

5. Sowers discloses:

> In a recent report . . . hypertensive patients who were taking β-blockers had a 28% higher risk of diabetes than did those taking no medication. In contrast, patients with hypertension who received thiazide diuretics, ACE inhibitors, or Ca^{2+} antagonists were found not to be at greater risk for subsequent diabetes than were patients who were not receiving any antihypertensive medications. However, that study was not prospective or randomized, and other randomized prospective trials have not shown an increase in the development of diabetes with β-blocker or low-dose diuretic treatment of hypertension.

(Id. (citations omitted).)

6. Sowers describes the results of the "HOPE trial [which] tested the hypothesis that ACE inhibitors in general, and ramipril in particular, have beneficial effects on vascular disease complications above and beyond their effects on blood pressure" (id. at 1055).
7. Sowers discloses that the results from the HOPE trial, and other studies, showed that "ACE inhibitor therapy can improve insulin sensitivity and also delay the development of diabetes in patients at high risk for the development of this disease" (id.).
8. Parissis describes a study that investigated the "the plasma activity of inflammatory mediators such as granulocyte-macrophage colony-stimulating factor (GM-CSF), C-C chemokines and soluble adhesion molecules, produced by monocyte-endothelial cell adhesive interaction, in patients with arterial hypertension (Parissis 13 (abstract)).
9. Parissis notes that "concentrations of neurohormones such as ET-1, are often elevated in patients with arterial hypertension . . . possibly representing a vicious circle operative in endothelial cell apoptosis, endothelial dysfunction and peripheral vasoconstriction" (id. at 17-18 (citations omitted)).

ANALYSIS

We find that the Examiner has the better position. Claim 1 recites a method of treating coronary obstruction or peripheral vasoconstriction in a patient in need thereof, by administering to that patient a compound of formula (I). As the Examiner points out, claim 1 does not, by its terms, exclude diabetics or obese persons from the patients being treated.

As the Examiner also points out, and Appellants do not dispute, the compounds of formula (I) were described by Liu as being useful for treating diabetes (FF 1-2). As the Examiner further points out, the prior art shows that there was considerable overlap between diabetic patients and patients suffering from cardiovascular diseases, including hypertension (FF 3, 4), which in turn has been linked to peripheral vasoconstriction (FF 9).

Thus, we agree with the Examiner that an ordinary artisan, prompted by Liu to administer the claimed compounds to diabetic patients, would have considered it obvious that a significant number of those diabetic patients would also suffer from cardiovascular diseases, given the teachings in Sowers. Further, given the significant overlap between diabetic and cardiovascular diseased patient sets, we also agree that an ordinary artisan would have been prompted by the cited references to administer the claimed compounds to a patient in need of treatment for coronary obstruction or peripheral vasoconstriction, as long as that patient had diabetes or was obese.

It may be true that the cited references' rationale for treating a patient within the patient population recited in claim 1 would have been for the purpose of treating diabetes, or obesity, rather than coronary obstruction or peripheral vasoconstriction per se. Nevertheless, it is well settled that obviousness is shown when the prior art suggests practicing the claimed subject matter, even if the rationale supplied by the prior art is different than the patent applicant's. See *KSR Int'l Co. v.* Teleflex Inc., 550 U.S. 398, 419 (2007) ("In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the

patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103.").

Thus, in the instant case, as discussed, the cited references suggest administering the claimed therapeutic agent to individuals within the claimed patient population.

We note that Sowers does not appear to suggest any necessary or clear cut connection between diabetes drugs and their efficacy against cardiovascular disorders (see FF 5-7). We also acknowledge Appellants' argument that a number of non-diabetic factors can induce cardiovascular disorders (Reply Br. 3). However, Appellants point to no evidence suggesting that a diabetic patient in need of treatment for the claimed cardiovascular disorders would fail to receive the inherent therapeutic benefit described in Appellants' Specification upon being administered a compound according to claim 1, merely because that patient was a diabetic.

We note that obviousness may not properly be based on inherency. See In re Rijckaert, 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("'That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.' Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection.") (quoting In re Spormann, 363 F.2d 444, 448 (CCPA 1966)).

We are not persuaded, however, that the Examiner's prima facie case rests on an improper hindsight recognition of the inherent cardiovascular-treating therapeutic effect of the compounds of formula (I) described in Appellants' Specification. Rather, the impetus for administering those compounds to patients in need of treatment for coronary obstruction or peripheral vasoconstriction would have been the art-recognized fact that the

intended recipients of those compounds, diabetics, were also known to suffer, in a very large proportion, from cardiovascular disorders.

In sum, for the reasons discussed, we agree with the Examiner that an ordinary artisan would have been prompted by the cited references to administer a compound according to formula (I) to individuals within the patient set recited in claim 1. We therefore affirm the Examiner's obviousness rejection of claim 1 over Liu, Sowers, and Parissis. The remaining claims fall with claim 1. See 37 C.F.R. § 41.37(c)(1)(vii).

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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